Bilateral Spermatic Vein Microligation and Human Chorionic Gonadotropin and Recombinant Folicle Stimulating Hormone Combination Therapy in Patient with Azoospermia

Gampo A. Irdam[1], Budi Wiweko[2], Ponco Birowo[1], Nur Rasyid[1], Akmal Taher[1]

[1]Department of Urology Cipto Mangunkusumo Hospital/Department of Surgery Faculty of Medicine Universitas Indonesia
[2]Department of Obstetrics and Gynecology Cipto Mangunkusumo Hospital/Faculty of Medicine Universitas Indonesia

Abstract

Azoospermia, the absence of spermatozoa in ejaculate due to testicular failure or reproductive tract obstruction, is the most unfavorable form of male infertility and is found in approximately 15% of infertile men. We report a 34 years old man with primary infertility for 4 years due to azoospermia. There were bilateral varicoceles grade 2, low level of serum testosterone and luteinizing hormone and normal level of serum folicle stimulating hormone (FSH) on the low margin. The patient underwent sperm extraction (PESA and TESE method) with result there were no motile spermatozoa. On the spermatogenesis examination, it was revealed that the spermatogenesis process stopped on the spermatid phase. We decided to perform bilateral spermatic vein microligation followed by hormonal injection (HCG and FSH recombinant) for 4 months. On the evaluation, there was motile spematozoa on the left PESA. This finding suggested the effectiveness of the therapy, there was a spermatogenesis on this patient after bilateral spermatic vein microligation and combination hormonal therapy of HCG and FSH recombinant for 4 months.
Keywords: *primary infertility, azoospermia, HCG, recombinant FSH, spermatic vein microligatio*n

Mikroligasi Vena Spermatika Bilateral, dan Terapi Kombinasi *Human Chorionic Gonadotropin* serta *Folicle Stimulating Hormone* Rekombinan pada Pasien dengan Azoospermia

Abstrak

Azoospermia, tidak adanya spermatozoa dalam ejakulat akibat kegagalan testis atau obstruksi saluran reproduksi, adalah bentuk paling menguntungkan pada infertilitas pria dan ditemukan sekitar 15% pada pria tidak subur. Kami melaporkan seorang pria berusia 34 tahun dengan infertilitas primer selama 4 tahun karena azoospermia. Terdapat varicocele bilateral tingkat 2, kadar testosteron serum dan luteinizing hormone rendah sedangkan kadar folicle stimulating hormone (FSH) normal pada nilai rendah rendah. Pasien menjalani ekstraksi sperma (metode PESA dan TESE) dengan hasil tidak ada spermatozoa motil. Pada pemeriksaan spermatogenesis, ditemukan bahwa proses spermatogenesis berhenti pada fase spermatid. Kami memutuskan untuk melakukan mikroligasi vena spermatika bilateral diikuti dengan injeksi hormon (HCG, dan FSH rekombinan) selama 4 bulan. Pada evaluasi, ada spematozoa motil pada PESA kiri. Temuan ini menunjukkan efektivitas terapi, yaitu terjadi spermatogenesis pada pasien mikroligasi vena spermatika bilateral dan terapi hormonal kombinasi HCG dan FSH rekombinan selama 4 bulan.
Keywords: ***infertilitas primer, azoospermia, HCG, FSH rekombinan, mikroligasi vena spermatika***

Introduction

Azoospermia is defined as the absence of spermatozoa in microscopic examination of centrifuged semen in two examinations.[1] Azoospermia was found in approximately 1% of men and 15% of infertile men.[2,3] This condition must be evaluated for its etiology in order to determine the existing risk factors, the prognosis and the appropriate management of the patient.

Generally azoospermia can be divided into 3 categories: pre-testicular, testicular and post-testicular. Pre-testicular abnormalities are hormonal disorders that affect the spermatogenetic process and are quite rare. The frequency of azoospermia caused by low gonadotropins was found to be less than 0.5% of cases. Testicular abnormalities are caused by failure of spermatogenetic process due to intrinsic abnormalities in the testis either primary, or due to some other process in the testis. Post-testicular abnormalities are caused by obstruction along the ejaculatory ducts or due to failure of the ejaculation process itself.[1,4]

The most common etiology found in azoospermia is varicocele, which is found in approximately 12%-20% of men. Varicocele is an abnormal dilatation of the pampiniform plexus that can cause failure of growth and development of the testes as well as the spermatogenesis process. There is still a debate about the direct relationship of varicocele with infertility, but some studies suggest that varicocele surgery or varicocelectomy were found to have therapeutic effects for both fertility and testicular development. [5-8]

In this paper, we will discuss one case of primary infertility in a male patient with bilateral varicocele and hypogonadism who showed a positive response to bilateral varicocelectomy and hormonal injection.

Case report

A man aged 34 years old came to the outpatient unit in March 2012 with a chief complaint of not having children at four years of marriage. There were no erection, penetration or ejaculation dysfunctions. The patient had sexual intercourse with his wife on a regular basis with a frequency of once per week. There was no history of diabetes mellitus, mumps, sexually transmitted diseases, reproductive tract infection, urinary tract infection, radiation and trauma. The patient did not smoke. There were no routine exposures to extreme temperatures. The development of secondary sex characteristics appeared to be fine. No identical abnormalities from the same side of the family and no abnormalities in the patient's wife were found.

Of the physical examination, the patient was in good condition. No ginecomastia and abnormal urethral orifice location were observed. Both testes were normal on palpation. Initial laboratory examination showed normal follicle stimulating hormone (FSH) level (low margin) and low luteinizing hormone (LH) and serum testosterone levels (Table 1). Sperm analysis showed azoospermia. Ultrasound performed on the patient demonstrated homogeneous structure for both testis, left testis size of 16.6 cm^3 and right testis size of 12.4 cm^3, a 0.65 cm cyst on the left epididymal head, left epididymal head enlargement, and widened bilateral pampiniform plexus.

Table 1. Testosterone Levels of Serum LH and FSH Before and After Therapy

	Before	After	Normal Range
Testosterone	1.06 ng/dl	6.74 ng/dl	2.8 – 8.0 ng/dl
LH	0.546 mIU/ml	< 0.1000 mIU/ml	0.5 – 9 mIU/ml
FSH	1.8 mIU/ml	1.7 mIU/ml	1 - 8 mIU/ml

In April 2012, the patient underwent *percutaneous epididymal sperm aspiration* (*PESA*) and *testicular sperm extraction (TESE)*. During the operation, no motile sperm from PESA aspirate or TESE tissue preparations were obtained (Table 2). Histopathological examination of biopsy tissue during TESE showed abnormal spermatogenesis process, which halted at the spermatid stage. A very minimal amount of spermatozoa were found in both testes.

Table 2. Characteristics of Microscopic Findings in PESA and TESE, April 2012

Parameter	Before Washing				After Washing			
	PESA		TESE		PESA		TESE	
	Right	Left	Right	Left	Right	Left	Right	Left
Volume	1.5 ml	2 ml	-	-	0.2 ml	0.2 ml	-	-
Motile sperm*	0	0	0	0	$7x10^5$ ml	$3x10^5$ ml	1/15 LP	1/10 LP
Immotile sperm	$7.7x10^6$ /ml	$20x10^6$ /ml	10/LP	10/LP	$47x10^6$ /ml	$67x10^6$ /ml	22/LP	20/LP
Concentration	$7.7x10^6$ /ml	$20x10^6$ /ml			$47.7x10^6$ /ml	$67,3x10^6$ /ml		
Motility	0 %	0 %	0 %	0 %	1.47%	0.45 %		

*Motile sperm in place only

It was decided that microligation of bilateral varicocele and combined hormonal injection therapy (HCG and recombinant FSH) would be given. Bilateral spermativc vein microligation was conducted in June 2012 followed by HCG and recombinant FSH injections given for 4 months. HCG was given 1000 IU for the first 2 months three times a week. The dosage was adjusted to 2500 IU for the next 2 months. Recombinant FSH was given 75 IU for the first 2 months three times a week, and the dosage was also adjusted to 150 IU for the next 2 months.

Post bilateral spermati vein microligation and hormonal injections, sperm analysis were performed again with more or less the same results as before therapy. It was decided to execute PESA and TESE. In the operations conducted in October 2012, motile sperm in the left PESA were found. The couple underwent intra cytoplasmic sperm injection on November 2012 and currently the wife has already been conceived for 26 weeks.

Discussion

Infertility is a common problem. In the United States, approximately 15% of couples experience infertility, about 50-60% of it is attributable to the male factor.[1] Azoospermia, the absence of spermatozoa in the semen as a result of testicular failure or obstruction of the reproductive tract, is the most severe form of infertility in men.[9]

Classification of azoospermia is generally divided into three: pre-testicular, testicular and post-testicular.[1] In this patient, the possible risk factors for azoospermia were bilateral varicoceles (testicular factor) and low levels of testosterone and LH (pre-testicular factor).

Up to now there is a difference of opinions about the relationship between varicocele and fertility. Some stated that there is no association between varicocele and fertility. Uehling,[10] found 25% of varicocele in 440 married men. There were no differences in fertility in married men group (31%) and unmarried men group (32%). In a research on the characteristics of sperm in men with varicocele and without varicocele carried by Lund and Larsen,[11] there were no differences in the number and motility of sperm, the percentage of normal sperm and the fecundity.

Opposite opinion stated that a varicocele could cause testicular damage that plays a role in infertility. There is a clear relationship between varicocele and reduced male fertility, but few studies provide results that varicocele is associated with semen abnormalities, decreased testicular volume and decreased Leydig cell function.[12,13]

In this patient, varicocele surgery with bilateral spermatic vein microligation techniques was performed. Surgery on varicocele showed a positive effect, including improvement on the development of the testes, restoration of spermatogenesis function and increased fertility.[13-15] In a literature review conducted by Cayan et al,[16] microscopic varicocelectomy techniques yield higher spontaneous pregnancy rates, lower recurrence and lower possible complications of hydrocele than conventional techniques.

The cause of azoospermia in this patient was also considered to be pre-testicular factor. The patient suffered from hypogonadotropic hypogonadism. Preliminary examination showed low serum testosterone and luteinizing hormone levels (Table 1). Low serum testosterone levels alone can be primary or secondary. Testicular abnormalities in primary hypogonadism can be

caused by several etiologies, which comprise of genetic abnormalities (klinefelter syndrome as the most frequent), exposure to toxins or chemotherapy, congenital defects (anorchia or cryptorchidism), history of orchitis, history of trauma or torsion, drugs or increased testicular temperature (due to other reasons, such as varicocele).[17,18]

Secondary hypogonadism caused by disturbance in the hypothalamic-pituitary-gonadal axis can be congenital abnormalities such as kallman's syndrome (anosmia and GnRH deficiency) and GnRH receptor deficiency and mutations, but can also be acquired, such as drugs, excess estrogen, diabetes mellitus, obesity and its related morbid conditions, hyperprolactinemia, old age, history of trauma and radiation, as well as other causes.[17,19-23] Low testosterone level in this patient were not thought as a result of the varicocele. Testicular abnormalities with low testosterone level will produce in a positive feedback on the pituitary and hypothalamus, thus will increase gonadotropin. Instead, in this patient a low luteinizing hormone level were obtained. Nevertheless, the risk factors for the hypogonadotropic hypogonadism state in this patient were not found.

Hypogonadotropic hypogonadism in this patient were treated by giving a combination hormone of the HCG and recombinant follicle stimulating hormone. HCG is a therapeutic option in low testosterone level because this hormone can stimulate the Leydig cells in secreting testosterone which will then increase spermatogenesis.[24] In a clinical study, it was found that HCG can stimulate spermatogenesis in patients with azoospermia. With HCG therapy without another hormone combination, the spermatogenesis process can be maintained even though the sperm count may be reduced over time.[25] The state of falling sperm counts can be overcome by administering FSH.[25] Of a case report by Yong et al, a therapeutic effect on spermatogenesis and fertility were obtained from the combination of HCG and HMG (human menopausal gonadotropin) three times per week for 16 months. [26]

The effectiveness of the combination of HCG and recombinant FSH had been demonstrated by a prospective study.[27] Ten men with gonadotropin deficiency and low testosterone were given HCG therapy for 3-6 months and recombinant FSH for 18 months. Seven men showed presence of spermatogenesis process in 6 months and achieved the target number of sperm in 9 months FSH therapy. Three of the seven men can impregnate their partners. There was an increase in testicular volume. The study concluded that the combination of recombinant FSH and HCG is effective in the induction of spermatogenesis and fertility in patients with hipogonadotropin.[27]

In this patient, sperm aspiration was redone after HCG and recombinant FSH injection therapy. Positive results were found in the form of motile sperm in the left PESA. This showed the success of therapy in the form of the presence of spermatogenesis process in the patient after 4 months of hormonal therapy. Further follow-up is still needed on this patient to assess whether the spermatogenesis continued and become progressively adequate, as demonstrated by the achievement of the target number of sperm and the occurrence of pregnancy in the patient's partner.

Conclusion

There is a positive response in the form of the occurence of spermatogenesis on azoospermic male after bilateral spermatic vein microligation follwed by combination hormonal therapy of HCG and recombinant FSH for 4 months. Further follow ups are still needed to evaluate the continuity and improvement of spermatogenesis process.

References

1. Jarow J, Sigman M. The evaluation o the azoospermic male: AUA best practice statement. American Urological Association, 2010.
2. Willott GM. Frequency of azoospermic. For sci inter. 1982; 20:9.
3. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of he azoospermic patient. J Urol 1989; 142:62
4. Ezeh UIO. Beyond the clinical classification of azoospermia. Human reprod. 2000;15:2356-9.
5. Edey AJ, Sidhu SP. Male infertility: role of imaging in the diagnosis and management. Imaging 2008; 20: 139-46
6. Kumanov P, Ralista N, Tomova R, Tomova A. Adolescent varicocele: who is at risk? Pediatrics. 2008;121.
7. Rebnon JB, Carey P, Prior JL. Varicocele the most common cause of male factor infertility? Human reprod. 2002; 8: 53-8.
8. Cayan S, Shavakhabov S, Kadioglu A. Treatment of palpable varicocele in infertile men: a meta analysis to define the best technique. J androl. 2009;30:33-40.
9. Safran A, Reubinoff BE, Katz AP et al. Assisted reproduction for a treatment of azoospermia. Human reprod. 1998;13.

10. Uehling DT. Fertility in men with varicocele. Int J Fertil. 1968;13:58-60.
11. Lund L, Larsen SB. A follow up study of semen quality and fertility in men with varicocele testis and in control subjects. Br J Urol. 1998;82:682-6.
12. Dohle GR, Colpi GM, hargreave TB, Papp GK, Jungwirth A, Weidner W. EAU guidelines on male infertility. European urology. 2005;48:703-11.
13. Jarow JP. Effects of varicocele in male infertility. Hum Reprod Update. 2001; 7: 59-64
14. Ficarra V, Cerruto MA, Ligouri G, Mazzano G, Minucci S, Tracia A, Gentile V. Treatment of varicocele in subfertile men: the cochrane review- a contrary opinion. Eur urol. 2006;49:258-63.
15. Kass EJ, Belman AB. Reversal of testicular growth failure by varicocele ligation. J urol. 1987; 137:476-8.
16. Laven JS, Haans LC, et al. Effects of varicocele treatments in adolescents: a randomized study. Fertil steril. 1992;58:756-62.
17. Cayan S, Shavakhabov S, Kadioglu A. Treatment of palpable varicocele in infertile men: a meta analysis to define the best technique. J androl. 2009;30:33-40.
18. Pantalone KM, Faiman C. Male hypogonadism: more than just a low testosterone. Cleveland clinic journal of medicine. 2012;79.
19. Sikka SC, Swerdloff RS, Rajfer J. In vitro inhibition of testosterone biosynthesis by ketoconazole. Endocrinology. 1985:116;1920-5.
20. Pallais JC, Au M, Pitteloud N, Seminara S, Crowley WF Jr. Kallmann syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, eds. GeneReviews. Seattle, WA: University of Washington; 1993.
21. Chevrier L, Guimiot F, de Roux N. GnRH receptor mutations in isolated gonadotropic deficiency. Mol Cell Endocrinol. 2011;346:21-8.
22. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. J Clin Endocrinol Metab. 2011; 96:2341-53.
23. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care. 2010; 33:1186-92.
24. Grossmann M, Gianatti EJ, Zajac JD. Testosterone and type 2 diabetes. Curr Opin Endocrinol Diabetes Obes. 2010;17:247-56.
25. Behre HM, Nieschlag E, Meschede D, Partsch CJ. Diseases of the hypothalamus and the pituitary gland. Andrology: male reproductive health and dysfunction. 2nd ed. Berlin: Springer-Verlag; 2000. p.125-42.
26. Depenbusch M, Eckardstein SV, Simoni M. Maintenance of spermatogenesis in hypogonadotropic hypogonadal men with human chorionic gonadotropin alone. European journal of endocrinology. 2002; 147: 617-24.
27. Yong EL, Lee KO, Ng SC, Ratnam SS. Induction of spermatogenesis in isolated hypogonadotrophic hypogonadism with gonadotrophns and early intervention with intracytoplasmic sperm injection. Human reproduction. 1997;12:1230-2.
28. Liu PY, Turner L, Rushford D, et al. Efficacy and safety of recombinant human folicle stimulating hormone (gonal F) with urinary human chorioncic gonadotrophin for induction of spermatogenesis and fertility in gonadotrophin deficient men. Human reproduction. 1999;14: 1540-55.